IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CELLECTIS S.A.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 11-173-SLR
	)	
PRECISION BIOSCIENCES, INC. AND PRECISION PLANTSCIENCES, INC.,	)	
	)	
Defendants.	)	

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Richard L. Horwitz, Esquire and David E. Moore, Esquire of Potter Anderson & Corroon LLP, Wilmington, Delaware. Counsel for Defendants. Of Counsel: David B. Bassett, Esquire, and Vinita Ferrera, Esquire, Esquire of Wilmer Cutler Pickering Hale and Dorr LLP.

MEMORANDUM OPINION

Dated: April 9, 2013
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

Plaintiff Cellectis S.A. ("Cellectis") filed the present action against defendant Precision Biosciences, Inc. ("Precision") on March 1, 2011, alleging infringement of U.S. Patent No. 7,897,372 ("the '372 patent"), which is assigned to Cellectis. (D.I. 1) Precision answered the complaint on March 23, 2011 and counterclaimed against Cellectis for non-infringement and invalidity of the '372 patent. (D.I. 10) Cellectis answered the counterclaims on April 18, 2011. (D.I. 21) Cellectis amended the complaint the same day, alleging unfair competition and violations of the Lanham Act, 15 U.S.C. § 1125(a), each relating to allegedly false and misleading commercial representations on Precision's website. (D.I. 22) On May 5, 2011, Precision answered the amended complaint, adding a third affirmative defense that Cellectis is barred from relief "in whole or in part by laches, estoppel and/or other equitable doctrines," and asserting counterclaims. (D.I. 27) On June 3, 2011, Cellectis answered the counterclaims in the amended answer. (D.I. 28) Precision's motion for leave to amend its answer and counterclaims to add allegations of inequitable conduct in the procurement of the '372 patent was denied. (D.I. 113; D.I. 170) On October 24, 2012, after leave to file an amended complaint adding Precision PlantSciences, Inc. (hereinafter, collectively with Precision Biosciences, Inc., "Precision") as a defendant was granted (D.I. 202), Cellectis filed a supplemental amended complaint (D.I. 203), which Precision answered on November 14, 2012 (D.I. 205).

Presently before the court are several motions for summary judgment: Cellectis' motion for summary judgment of infringement (D.I. 222) and Precision's cross-motion

for summary judgment of no literal infringement of the '372 patent (D.I. 227); and Cellectis' motion for summary judgment of no invalidity for anticipation (D.I. 233). Cellectis' motion to exclude testimony by Precision's expert is also pending. (D.I. 231) The court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

II. BACKGROUND

A. Parties

Cellectis is a publicly-traded biotechnology company in the field of genetic engineering, particularly in the use of meganucleases as innovative tools to enable targeted modifications to DNA. (D.I. 22 at ¶¶ 10-11; D.I. 27 at 7 ¶ 7) Cellectis was founded in 1999 and is incorporated and headquartered in France. (D.I. 22 at ¶¶ 1, 10)

Precision is a privately-held biotechnology company that also has as its focus the development and commercialization of engineered endonucleases. (D.I. 27 at 6 ¶ 6) It was founded in 2006 and is a Delaware corporation with its principal place of business in North Carolina. (D.I. 22 at ¶ 2; D.I. 27 at 6 ¶¶ 1,6)

B. The '372 Patent

The '372 patent, entitled "I-*Cre*I Meganuclease Variants with Modified Specificity, Method of Preparation and Uses Thereof," is directed to particular mutated I-CreI[1] meganucleases that bind and cleave DNA at specific sites. (D.I. 1 at ¶ 8 & ex.1) The '372 patent issued from U.S. Patent Application Serial No. 11/908,798 ("the '798 application"), the U.S. phase application under 35 U.S.C. § 271 of PCT No. PCT/IB2006/001203, filed March 15, 2006 (hereinafter, the "Parent PCT"). The Parent

[1]The court follows the parties' nomenclature, where I-CreI is not italicized.

PCT, in turn, claimed priority to two foreign applications: (1) PCT/IB2005/000981 (March 15, 2005); and (2) PCT/IB2005/003083 (September 19, 2005). The '372 patent names two inventors: Philippe Duchateau and Frederic Paques.

For the present motions, Cellectis asserts that Precision infringes claim 40, which depends from claim 37 (D.I. 223 at 4), and that claims 37, 40, 42, 44, 46, 50, and 52 are not anticipated (D.I. 234 at 1).

III. CLAIM CONSTRUCTION

Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification and prosecution history - because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

A. "[M]onomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32,33 and 38 modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets"

The court declines to construe the first phrase of independent claim 37, "monomer of an I-CreI meganuclease variant," without the context of the remainder of the claim. While the term comprising is open-ended, the Federal Circuit has held that the term "comprising" may not alter the scope of the claim. *Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1380 (Fed. Cir. 1998) ("'Comprising' is not a weasel word with which to abrogate claim limitations.'"). The patent specification teaches that "other mutations that do not alter the cleavage activity of the variant are not indicated and the nomenclature here does not limti the mutations to the only three positions 44, 68, and 70." ('372 patent, 5:51-54; *see also* 17:4-14 (describing a variant as "contain[ing] mutations that do not alter its activity"))

In light of the specification, the court finds that the claim does not encompass

limitless mutations[2] and, instead, construes this limitation to mean: "A polypeptide of an I-CreI meganuclease variant, which polypeptide has the amino acid sequence of SEQ ID NO: 70 in which from 1-3 of the amino acids corresponding to positions 44, 68, and 70 of wild-type I-CreI and from 1-6 of the amino acids corresponding to positions 26, 28, 30, 32, 33, and 38 of wild-type I-CreI have been substituted with different amino acids. The claimed polypeptide, when in a dimeric form, is able to cleave DNA. Consistent with the word 'comprising,' the scope of the claim may include other mutations that do not alter the cleavage activity of the variant."

The parties have defined "monomer" as "a molecular building block - e.g. a polypeptide - that can be associated with another to form a larger molecule." (D.I. 164) Precision's expert now explains that a single-chain meganuclease includes two domains (not monomers) in order to separate the terms "monomer" and "domain."[3]

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[2]As suggested by Cellectis in its proposed construction:

> [M]onomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO:70, wherein said at least one mutation comprises a substitution at one or more of the amino acid residues at positions 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code lg9y and said monomer further comprises at least one additional mutation of an amino acid residue at positions 26, 28, 30, 32, 33 or 38 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code lg9y.

(D.I. 179 at 11-12)

[3]Dr. Seligman explains: "While the language of claims . . . recites single-chain chimeric meganucleases that comprise a 'monomer' . . . it is my opinion that single-chain (di-LAGLIDADG) I-CreI meganucleases comprise mono-LAGLIDADG I-CreI domains, not monomers . . . ." (D.I. 128 at ex.1 ¶ 66 n.4) Precision's explanation

(D.I. 128 at ex.1 ¶ 66 & n.4; D.I. 230 at ¶¶ 11-15) The difference in usage of these terms is not clear cut. When describing the heterodimeric form, the patent specification refers to an I-DmoI monomer (I-DmoI is considered a single-chain meganuclease). ('372 patent, 6:61-7:3) The specification also refers to a heterodimer as "a single-chain chimeric molecule consisting of the fusion of two different I-CreI variants . . . [or] two separate monomers chosen from two different I-CreI variants . . . ." ('372 patent, 10:26-21) Several of the scientific references cited in the record indicate that one of skill in the art would understand the '372 patent to teach a single-chain meganuclease made up of two "monomers" to be the same as one made up of two "domains."[4] (*See e.g.*, D.I. 178 at exs. E and G) For these reasons, the court construes monomer to be "a molecular building block - e.g., a polypeptide - that can be covalently or non-covalently

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of these terms is targeted towards convincing the court of the validity of its proposed claim construction of "monomer of an I-CreI meganuclease variant" as "one of two polypeptides, each having a single copy of the dodecapeptide (LAGLIDADG) motif, **that can act together to form an I-CreI variant homodimer**." (D.I. 177 at 6-7 (emphasis added)) The court declined to construe this term separately and has not limited claim 37 to a homodimer.

[4]Using I-CreI, a homodimer, and I-DmoI, a single-chain protein, researchers described an "axis separat[ing] two monomers or apparent domains" and designed "a novel meganucleases . . . by domain swapping or fusion of homing endonuclease domains." (D.I. 178 at ex. G, Jean-Charles Epinat et al., *A novel engineered meganuclease induces homologous recombination in yeast and mammalian cells*, 31(11) Nucleic Acids Research, 2952, 2952-53 (2003)) Another article has described generating "an artificial highly specific endonuclease by fusing domains of homing endonucleases I-DmoI and I-CreI." Specifically, "the N-terminal domain of I-DmoI [was fused] to an I-CreI monomer." (D.I. 178 at ex. E, Brett S. Chevalier et al., *Design, activity, and structure of a highly specific artificial endonuclease*, 10 Molecular Cell 895, 895 (2002))

bonded with another to form a larger molecule."[5]

The above construction is consistent with the court's construction of the phrase "when in a dimeric form," which the parties have defined as "when two monomers are associated." (D.I. 164) The patent specification and the claims contemplate meganucleases which are homodimers and heterodimers, as well as single-chain meganucleases (covalently bonded). ('372 patent, 10:22-33, 11:21-23; *see e.g.* claims 6, 12 & 13) The court, therefore, construes the phrase "when in a dimeric form" to mean "when two monomers are either covalently or non-covalently bonded."[6]

B. "[M]odified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets"

Cellectis' construction of this limitation adds ambiguous language, "where the DNA target cite is not cleaved in the same conditions by an initial meganuclease scaffold," and ignores the inclusion of SEQ ID NO: 70 in the claim. (D.I. 179 at 13-14) Precision's construction attempts to recite all of the nucleotide permutations in the triplets, resulting in a complicated formula which will not be helpful to a jury. Accordingly, the court construes this limitation to mean "having DNA cleavage specificity for a set of targets that differs from the targets cleaved by SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets."

C. "A single-chain chimeric meganuclease comprising [a] fusion of [two

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[5]By this definition, the court equates Precision's use of the term "domain" to the term "monomer."

[6]This construction resolves the parties' dispute over the meaning of the word "associated." (D.I. 228 at 13-14; D.I. 246 at 8-9)

monomers]"

The parties' proposed constructions differ by one word, protein versus polypeptide. Cellectis proposes "[a] meganuclease in the form of a single **protein** comprising a first monomer fused to a second monomer," while Precision proposes "[a] meganuclease in the form of a single **polypeptide** comprising a first monomer fused to a second monomer." As the term polypeptide is more consistent with the claim limitations, the court adopts Precision's construction.[7]

D. "[V]ariant of the wild-type monomer from I-CreI"

Cellectis argues that the above limitation would be understood by one of skill in the art, according to the plain language of the claims, to be "a mutant monomer of I-CreI, which when in dimeric form, retains the ability to cleave DNA;" Precision asserts that the term is indefinite. (D.I. 179 at 18-19; D.I. 177 at 26-27) The definiteness requirement is rooted in § 112, ¶ 2, which provides that "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." "A determination of claim indefiniteness is a legal conclusion that is drawn from the court's performance of its duty as the construer of patent claims." *Personalized Media Comm., LLC v. Int'l Trade Com'n*, 161 F.3d 696, 705 (Fed. Cir. 1998).

> Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention,

[7]By its construction, the court does not suggest that the resulting "single-chain chimeric meganuclease" is itself a monomer.

§ 112 demands no more.

Id. (citing *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)). Claims that are not amenable to construction or are insolubly ambiguous are indefinite. *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008). As with every construction issue, the focus of the indefiniteness inquiry is on the meaning that claim terms would have to one of ordinary skill in the art "at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1313 (citing *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). Even if a claim term's definition can be reduced to words, it "is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope." *Halliburton*, 514 F.3d at 1251. In this regard, a claim term is indefinite if the patent does not provide an "objective anchor" or "yardstick against which potential infringers may measure their activities." *Girafa.com v. IAC Search & Media, Inc.*, Civ. No. 07-787, 2009 WL 3074712, at *2 (D. Del. Sept. 25, 2009).

Cellectis' expert, Dr. Edgell, explains that a "variant" would differ from I-CreI in that it would "contain[] mutations and/or substitutions resulting in 'modified specificity' while retaining its cleavage ability." In his opinion, "the '372 specification teaches that variant I-CreI meganucleases of the invention have at least substitutions at 44, 68 and/or 70 (as well as the other specified mutations and/or substitutions) and are capable of targeting sequences having alterations in the target site at positions ±5-3, and have cleavage activity." (D.I. 185 at ¶ 47) Precision's expert, Dr. Seligman,

explains that

> some of skill in the art might draw an arbitrary line between a naturally-occurring protein and a recombinant protein at a certain percentage identity between their amino acid sequences, and declare that beyond a certain percentage the proteins are so different as to no longer be variants of each other. . . . [T]he determination would not be made based upon a particular percentage, but upon a "gut reaction" that two proteins are similar enough or different enough that the term variant should or should not be used. . . . [O]ne of skill in the art would view the percentage of substitutions as less relevant than the nature of the substitutions, and how they affected the structure and function of the protein. Thus, . . . there is no single, clear, distinct or fixed meaning of the term "variant" as it would have been used by those of skill in the art in 2005 or 2006.

(D.I. 178 at ¶ 66)

While the patent specification uses the terms "mutant" and "variant," it does not define or use the term "variant of the wild-type monomer from I-CreI." Cellectis' proposed description of a "variant" does not apprise one of skill in the art of the scope of the claim. Dr. Edgell's explanation of the term allows for limitless mutations and does not identify how one of skill in the art would identify the "variants" containing mutations which would still retain cleavage ability. As Dr. Seligman explains, there would also be no clear delineation of when a monomer was no longer a "variant," but a different monomer. Even Cellectis, through its proposed construction, has not been able to reasonably apprise a person of skill in the art of the scope of the claim. The court concludes that the limitation "variant of the wild-type monomer from I-CreI" is indefinite.

IV. STANDARD OF REVIEW

"The court shall grant summary judgment if the movant shows that there is no

genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The moving party bears the burden of demonstrating the absence of a genuine issue of material fact. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 415 U.S. 574, 586 n.10 (1986). A party asserting that a fact cannot be—or, alternatively, is—genuinely disputed must support the assertion either by citing to "particular parts of materials in the record, including depositions, documents, electronically stored information, affidavits or declarations, stipulations (including those made for the purposes of the motions only), admissions, interrogatory answers, or other materials," or by "showing that the materials cited do not establish the absence or presence of a genuine dispute, or that an adverse party cannot produce admissible evidence to support the fact." Fed. R. Civ. P. 56(c)(1)(A) & (B). If the moving party has carried its burden, the nonmovant must then "come forward with specific facts showing that there is a genuine issue for trial." *Matsushita*, 415 U.S. at 587 (internal quotation marks omitted). The court will "draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000).

To defeat a motion for summary judgment, the non-moving party must "do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita*, 475 U.S. at 586-87; *see also Podohnik v. U.S. Postal Service*, 409 F.3d 584, 594 (3d Cir. 2005) (stating party opposing summary judgment "must present more than just bare assertions, conclusory allegations or suspicions to show the existence of a genuine issue") (internal quotation marks omitted). Although the "mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly

supported motion for summary judgment," a factual dispute is genuine where "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 411 U.S. 242, 247-48 (1986). "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-50 (internal citations omitted); *see also Celotex Corp. v. Catrett*, 411 U.S. 317, 322 (1986) (stating entry of summary judgment is mandated "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial").

V. DISCUSSION

A. Infringement

1. Standard

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Direct infringement requires a party to perform each and every step or element

of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007), *overruled on other grounds by* 692 F.3d 1301 (Fed. Cir. 2012). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

When an accused infringer moves for summary judgment of non-infringement, such relief may be granted only if one or more limitations of the claim in question does not read on an element of the accused product, either literally or under the doctrine of equivalents. *See Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *see also TechSearch, L.L.C. v. Intel Corp.*, 286 F.3d 1360, 1369 (Fed. Cir. 2002)

("Summary judgment of noninfringement is ... appropriate where the patent owner's proof is deficient in meeting an essential part of the legal standard for infringement, because such failure will render all other facts immaterial."). Thus, summary judgment of non-infringement can only be granted if, after viewing the facts in the light most favorable to the non-movant, there is no genuine issue as to whether the accused product is covered by the claims (as construed by the court). *See Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1304 (Fed. Cir. 1999).

2. Analysis

Cellectis asserts that Precision's COT 5.1/6.1 meganuclease[8] ("COT 5.1/6.1") literally infringes claim 40 of the '372 patent. (D.I. 223 at 2) Claims 37 and 40 read:

> 37. A recombinant monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32, 33 and 38, wherein said monomer when in a dimeric form is able to cleave DNA.
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> 40. The monomer of an I-CreI meganuclease variant of claim 37, wherein said monomer when in a dimeric form has a modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO:70 in at least one nucleotide in the +/- 3 to 5 triplets.

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[8]Cellectis avers that Precision's COT 5.1/6.1 meganuclease is "an engineered single-chain meganuclease variant made up of two engineered monomers, COT 5.1 and COT 6.1, joined by a linker peptide." (D.I. 223 at 8) Precision disagrees and states that it is "a di-LAGLIDADG meganuclease where the two I-CreI domains are connected by a polypeptide segment." (D.I. 228 at 11)

('372 patent, 68:37-48, 55-59) Comparing the COT 5.1/6.1 to claim 40, Cellectis argues that it is a recombinant monomer (COT 5.1) fused to another recombinant monomer (COT 6.1) forming a single-chain meganuclease. (D.I. 223 at 11) Further, COT 6.1 contains the "at least" two mutations contemplated by claim 37.[9] (D.I. 223 at 11-12) COT 5.1/6.1 is able to cleave DNA (D.I. 223 at 13) Finally, COT 5.1/6.1 has a modified DNA cleavage specificity relative to I-CreI in at least one nucleotide in the ± 3 to 5 triplets.[10] (D.I. 223 at 14)

Precision disputes that COT 6.1 has the amino acid sequence of SEQ ID NO: 70 with the recited substitutions, as there are "several significant differences" between the two sequences. (D.I. 228 at 18; D.I. 229 at ex.1 ¶¶ 80-83) Cellectis responds that SEQ ID NO: 70 is "a reference comparator for modified DNA cleavage specificity" and that SEQ ID NO: 70 is "a wild-type I-CreI." (D.I. 246 at 17-18) The parties' experts also disagree as to the meaning of the cleavage assays performed by Precision relative to each parties' proposed construction of claim 40. The court's construction of claim 37 allows "other mutations that do not alter the cleavage activity of the variant;" its construction of claim 40 includes "SEQ ID NO: 70" and does not include the ambiguous limitation "where the DNA target cite is not cleaved in the same conditions by an initial

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[9]At position 68 and 70, COT 6.1, has amino acids Y and S, whereas the wild-type I-CreI monomer has R and R. At position 26, COT 6.1 has amino acid A, whereas wild-type I-CreI has Q. (D.I. 224, ex. D. Belfort decl. at ¶¶ 46-52)

[10]COT 5.1/6.1 has TAT at -5 to -3 and AAG at +3 to +5, whereas wild-type I-CreI has GTC at -5 to -3 and GAC at +3 to +5. (D.I. 224, ex. D. Belfort decl. at ¶¶ 58-68)

meganuclease scaffold."[11] The disputes between the parties' experts as to the proper characterization of COT 6.1 raise genuine issues of material fact which must be resolved by a fact finder. Cellectis' motion for summary judgment is denied. Precision's cross-motion of no literal infringement is also denied.[12]

B. Invalidity for Anticipation

1. Standard

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *Key Pharms. v. Hercon Labs Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *Id.* A finding of anticipation will invalidate the patent. *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998).

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir.1991). In determining whether a patented invention is

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[11]By its construction of "monomer" and "when in dimeric form," the court has rejected Precision's arguments that COT 6.1 is a domain, not a monomer, and that COT 6.1 is not "in a dimeric form" when covalently linked in the COT 5.1/6.1 meganuclease. *See supra* part III.A; (D.I. 228 at 13-16)

[12]Precision argues that there is no literal infringement under its much narrower proposed construction. As the court did not adopt Precision's proposed construction, the court does not herein address the substantive arguments.

explicitly anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted if needed to impart clarity or to avoid ambiguity in ascertaining whether the invention is novel or was previously known in the art. *Id.* The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *Id.* That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. V. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

2. Analysis

Cellectis argues that Seligman (2002)[13] does not anticipate the asserted claims

[13]"Seligman (2002)" is Lenny M. Seligman, et al., *Mutations altering the cleavage specificity of a homing endonuclease*, 30(17) Nucleic Acids Research, 3870 (2002).

of the '372 patent, as it does not disclose the "at least two mutations at the prescribed positions," 44, 68, or 70 and 26, 28, 30, 32, 33, or 38. (D.I. 234 at 3, 8) Precision responds that, although Seligman (2002) does not describe an experiment making a variant with substitutions at the two positions prescribed by claim 37, it "teaches the combination of mutations" and that "systematic substitution of the other seven amino acids that contact DNA" - which are at positions 26, 28, 30, 38, 44, 68, or 70 - may be made and "should reveal a large number of novel contacts." (D.I. 245 at 6 (citing Seligman (2002) at 3878)) Seligman (2002) showed variants made by substitutions at positions 32 or 33, as well as a variant made by a double substitution at 44 and 140. (D.I. 245 at 5-6)

As noted above, a prior art reference must disclose all of the limitations of the claim, "arranged or combined in the same way as in the claim," to anticipate a claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). If a prior art reference merely discloses a genus and the claim at issue recites a species of that genus, "the issue of anticipation turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could 'at once envisage' each member of the genus." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012) (citing *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)).

Seligman (2002) teaches a genetic approach used "in identifying homing endonucleases that recognize and cleave novel target sequences," and identifies the nine amino acids which make important direct contacts with DNA. It discloses mutants which have one of the two required substitutions and one mutant with a double

substitution. Further, it teaches that other substitutions and combination of substitutions are possible.[14] Seligman (2002) at 3870, 3872, 3878. The question for purposes of anticipation is whether the specific substitutions recited by claim 37 would be "immediately apparent to one of ordinary skill in the art." *Wrigley*, 683 F.3d at 1361 (citing *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (distinguishing cases in which a prior art reference discloses a genus versus those in which it discloses a number of species as part of a list)). It is also important to consider whether Seligman (2002) merely invites others to conduct further experimentation. *See Metabolite Labs., Inc. v. Lab. Corp. of America Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (holding that [a]n invitation to investigate is not an inherent disclosure).

The court concludes that there is a genuine issue of material fact as to whether Seligman (2002) expressly discloses all of the claim limitations and whether the specific substitutions would be apparent to one of skill in the art. Therefore, Cellectis' motion for summary judgment of no invalidity for anticipation is denied.

C. Expert Testimony

1. Standard

Cellectis requests that the court exclude the testimony on best mode of Precision's expert, Dr. Seligman, for lack of specialized knowledge; on obviousness as legally deficient; and on infringement, as based on a claim construction that departs from adjudicated constructions or accepted meanings. (D.I. 243 at 5-6) Rule 702 of

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[14]Specifically, "a systematic search of the remaining I-CreI DNA contacts should reveal a large number of novel contacts. Appropriate amino acid substitutions can then be combined to generate I-CreI derivatives that are specific for DNA sequences containing the appropriate cognate bases." Seligman (2002) at 3878.

the Federal Rules of Civil Procedure allows a qualified witness to testify in the form of an opinion if the witness' "scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue," and if his/her testimony is the product of reliable principles and methods which have been reliably applied to the facts of the case. An expert's opinion is reliable if it is "based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation;' the expert must have 'good grounds' for his or her belief." *In re Paoli Railroad Yard PCB Litigation*, 35 F.3d 717, 742 (3d Cir. 1994) (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993)).

Rule 702 also requires that the expert testimony must fit the issues in the case. In other words, the expert's testimony must be relevant for the purposes of the case and must assist the trier of fact. The Supreme Court explained that "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility." *Daubert*, 509 U.S. at 591-92. This standard, nevertheless, is not intended to be a high one or to be applied in a manner that requires parties "to prove their case twice - they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are correct, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (2000) (citing *Paoli*, 35 F.3d at 744).

Whether a best mode exists "is a question of fact composed of two subsidiary factual inquiries." *Bayer AG v. Schein Pharms., Inc.*, 301 F.3d 1306, 1320 (Fed. Cir.

2002). Did the inventor, at the time of filing the application, possess "a best mode for practicing the invention." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 963 (Fed. Cir. 2001). The first prong "is highly subjective and focuses on the inventor's state of mind as of the date of filing the application." *Bayer*, 301 F.3d at 1320. Next, if the inventor contemplated a best mode, then "[t]he second inquiry is whether the inventor's disclosure is adequate to enable one of ordinary skill in the art to practice the best mode of the invention. This inquiry is objective and depends upon the scope of the claimed invention and the level of skill in the relevant art." *Bayer*, 301 F.3d at 1320 (citing *Telecom Ltd. v. Samsung Elec. Co.*, 215 F.3d 1281, 1286 (Fed. Cir. 2000)).

2. Analysis

Dr. Seligman seeks to testify that, shortly after the '372 patent application was filed, the inventors published two articles "on the construction and evaluation of libraries of meganuclease variants." (D.I. 243 at 8) Cellectis asserts that this inference is improper as the earliest of the two publications was published six months after the patent-in-suit was filed and Dr. Seligman references no other document to support his theory. (D.I. 243 at 8)

Logically, research papers must lag behind actual research (especially peer reviewed publications). The court concludes that Dr. Seligman's opinions (D.I. 235 at ¶¶ 266-270) are not unreliable or unhelpful, when measured by the relatively low standard at this stage of the proceedings, coupled with the highly subjective nature of the state of mind inquiry.

Cellectis next argues that Dr. Seligman's testimony on obviousness does not

include a basis of motivation to combine and did not properly consider all of the evidence known to him; instead, he offers only insufficient conclusory statements. (D.I. 253 at 3-4) An obviousness inquiry requires a determination of "whether the claimed invention would have been obvious as a legal matter, based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness." *See Oxford Gene Tech. Ltd. v. Mergen, Ltd.*, 345 F. Supp. 2d 431, 435–36 (D. Del. 2004) (citations omitted). Importantly, even if each limitation of an asserted claim is found in the prior art, "there must be a 'reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success.'" *Id.* at 436 (citations omitted).

Dr. Seligman presents a summary of the obviousness standard (D.I. 235 at ¶¶ 58-63); his analysis includes his opinions on secondary considerations and motivation to combine (*id.* at ¶¶ 306-327) and claim charts illustrating his findings (*id.* at exs. E & F). While Cellectis may disagree with Dr. Seligman's analysis and conclusions, the court concludes that, at most, this goes to the weight of the evidence, which is properly addressed via cross-examination.

Finally, Cellectis, before the issuance of the court's claim construction, argues that Dr. Seligman's opinions relating to "comprising" should be excluded as based on an improper interpretation of this term, in great part because Cellectis disagrees with Precision's proposed narrower construction. (D.I. 253 at 6-7) As the court did not adopt either parties' construction, the court declines to undertake a review of the

parties' testimony or expert reports at this juncture. *See supra* part III.A. At trial, any expert opinions based on a construction other than that which the court has construed herein will not be allowed.[15] The court declines to award Precision its costs.

VI. CONCLUSION

For the foregoing reasons, Cellectis' motion for summary judgment of infringement and Precision's cross-motion for summary judgment of no literal infringement of the '372 patent are both denied. Cellectis' motion for summary judgment of no invalidity for anticipation is denied. Cellectis' motion to exclude testimony by Precision's expert is also denied. An appropriate order shall issue.

[15]The court will address at the pretrial conference any need for further expert discovery in this regard.